Full Text PA-97-098

AUTOIMMUNITY: GENETICS, MECHANISMS, AND SIGNALING

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P.T.

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National Institute of Allergy and Infectious Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Arthritis, Musculoskeletal and Skin Diseases
National Institute on Aging
Office of Research on Women's Health, NIH

PURPOSE

The National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS), National Institute on Aging (NIA), and the Office of Research on Women's Health, National Institutes of Health (NIH) invite applications for new and innovative investigator-initiated basic and preclinical research into the immune responses underlying autoimmune disease and its regulation for preventive or therapeutic purposes. Three specific areas of emphasis are highlighted: 1) genetic susceptibility for autoimmune disease, including the MHC and other genetic loci; 2) role and regulation of co-stimulation of T cells in autoimmunity; and 3) signal transduction in the autoreactive response.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This PA, "AUTOIMMUNITY: GENETICS, MECHANISMS, AND SIGNALING" related to

the priority area of Diabetes and Chronic Disabling Diseases. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800).

ELIGIBILITY

Applications may be submitted by for profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Domestic and foreign institutions are eligible to apply for R01 grants. Foreign institutions are not eligible for FIRST awards (R29). Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISMS OF SUPPORT

Traditional research project grant (R01) AND FIRST award (R29) applications may be submitted in response to this announcement. Applications for R01 grants may request up to five (5) years of support; applications for R29 grants must request five years of support.

Responsibility for the planning, direction, and execution of the proposed research for all applicable mechanisms of support will be solely that of the applicant.

RESEARCH OBJECTIVES

Background

Autoimmune diseases result when the immune response is directed at the body's own tissues. Autoreactive immune responses may be initiated in response to either exogenous (from outside the body, such as a pathogen) or endogenous (from inside the body) antigens in the context of a genetic background susceptible to autoimmunity. Antigen is processed and presented to the T cell, whose response can be affected by the availability of co-stimulatory ligand-receptor interaction(s). The interaction of antigen with the T cell in the context of co-stimulatory signals results in activation of various signal transduction pathways (see below). In addition, the environment of this interaction, including cytokines present, amount and character of antigen present and co-stimulatory molecules, can affect the type of response and its intensity.

Autoimmune diseases are more common in families. More than one gene is thought to underlie this genetic susceptibility with one of the important genetic loci being the Major Histocompatibility Complex locus. Marked progress in mapping areas of genetic susceptibility has been made for some diseases, including insulin dependent diabetes mellitus and systemic lupus erythematosus. For these two diseases, several of the susceptibility genes map to overlapping regions of the chromosome suggesting that the same or similar genes may be involved in the development of these different diseases. The fine mapping and identification of the genes should allow the evaluation of the functional consequences of their gene products. Evaluation of the interaction of multiple genes and the environment in the development of the autoimmune phenotype can follow. Further understanding of this process in the development of autoreactive responses could lead to novel approaches for the prevention or therapy of autoimmune diseases.

Increasingly, basic research has emphasized the importance of more than one signal for the activation of T cells. The antigen-T cell receptor complex is primary, but equally, the presence or absence of other signals, called co-stimulation, can direct the interaction to the development of tolerance rather than activation. Blockade of the co-stimulatory signal has prevented the development of disease in animal models of multiple sclerosis, insulin dependent diabetes mellitus, and systemic lupus erythematosus. Recently, investigation of this path in ongoing autoimmune disease suggests that these molecules may be important in the perpetuation of the autoreactive response. The number of these co-stimulatory signals which have been identified is growing rapidly, initially including the B-7 family, and now expanded to include the CD40-CD40L family. With further understanding of the mechanisms, these molecules could be exploited to modulate the initiation or progression of autoimmune disease.

Finally, much progress has been made in defining the intracellular and extracellular signaling pathways that mediate the consequences of the immune response after interaction of antigen and the immune system. These include the secretion of cytokines, production of cytotoxic T cells, activation of phosphoprotein signaling cascades, activation or repression of transcription factors, activation of cell death pathways, including apoptosis, and inflammatory cascades. The final common pathways of damage include release of proteases, nitric oxide and superoxide production, antigen-antibody complexes, and cytokines. Further understanding of these pathways in the development and regulation of the response to autoantigens and in mediating autoimmune disease may allow development of effective and innovative therapies for autoimmune disease.

NIA has responsibility for supporting basic research and training in fundamental studies of immunology that relate to aging.

Research Objectives and Scope

The objective of this PA is to encourage the application of advances in basic immunology to understanding the pathogenesis and regulation of the immune response to self antigens, focusing specifically on genetic susceptibility, including the interaction of genes, role of co-stimulation of immune cells, mechanism of induction, perpetuation, and tissue injury in the autoreactive response. Further understanding of the pathogenic and regulatory processes of the autoreactive immune response should lead to new approaches for the prevention or treatment of autoimmune diseases. Examples of topics of research interest include, but are not limited to:

o characterization of loci of genetic susceptibility to autoimmune disease, including overlapping loci for multiple diseases; characterization of the genes in these loci and their products, including the functional role of these genes;

o mechanisms and interactions by which genes influence the susceptibility to development of autoimmune disease;

o characterization of the role of co-stimulatory molecules in the response to self antigens;

o identification of regulators (agonists and antagonists) of co-stimulatory molecules in the autoreactive response;

o the role of apoptosis in the pathogenesis of autoimmunity and autoimmune disease;

o the role of STAT proteins in the autoreactive immune response; potential for regulation of this response; and

o characterization of cytokine expression and regulation in response to self antigens

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are provided that

inclusion is inappropriate with respect to the health of the subjects of the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research", which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and the NIH Guide for Grants and Contracts, Vol. 23, No.11, March 18, 1994.

Investigators may obtain copies from these sources or from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application for PHS 398 (rev. 5/95) and will be accepted on the standard application deadlines as indicated on the application kit. Application kits are available at most institutional offices of sponsored research and may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone (301) 435-0714, email: asknih@odrockm1.nih.gov.

For purposes of identification and processing, item 2 on the face page of the application must be marked "YES". The PA number and the PA title must also be typed in section 2.

The completed, signed original and five (5) legible, single-sided copies of the application must be sent or delivered to:

DIVISION OF RESEARCH GRANTS
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817-7710 (for express/courier service)

R29 applications must include at least three sealed letters of reference attached to the face page of the original application. FIRST applications submitted without the required number of reference letters will be considered incomplete and will be returned without review.

Applicants from institutions that have a General Clinical Research Centers (GCRC) funded by the NIH National Center for Research Resources may wish to identify the Center as a resource for conducting the proposed research. If so, a letter of agreement from the GCRC Program Director must be included in the application material.

REVIEW CONSIDERATIONS

Review Procedures

Applications will be assigned on the basis of established PHS referral guidelines. Upon receipt, applications will be reviewed for completeness by the NIH Division of Research Grants. Incomplete applications will be returned to the applicant without further consideration. Applications will be reviewed for scientific and technical merit by study sections of the Division of Research Grants, NIH, in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council.

Review Criteria

The five criteria to be used in the evaluation of grant applications are listed below. To put those criteria in context, the following information is contained in instructions to the peer reviewers.

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. The reviewers will comment on the following aspects of the application in their written critiques in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered by the reviewers in assigning the overall score weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have a major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

1. Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

2. Approach. Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation. Does the project employ novel concepts, approaches or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

4. Investigator. Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

5. Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

The initial review group will also examine: the appropriateness of proposed project budget and duration; the adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research and plans for the recruitment and retention of subjects; the provisions for the protection of human and animal subjects; and the safety of the research environment.

AWARD CRITERIA

Applications will compete for available funds with all other favorably recommended applications. The following will be considered when making funding decisions: quality of the proposed project as determined by peer review, program balance, and availability of funds.

INQUIRIES

Written and telephone inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Inquiries regarding programmatic (research scope and eligibility) issues may be directed to:

Elaine Collier, M.D.
Division of Allergy, Immunology, and Infectious Diseases National
Institute of Allergy and Infectious Diseases 6003 Executive
Boulevard, Room 4A20
Bethesda, MD 20892-7640
Telephone: (301) 496-7104
FAX: (301) 402-2571
Email: ec5x@nih.gov

Joan T. Harmon, Ph.D.
Chief, Diabetes Research Section
National Institute of Diabetes and Digestive and Kidney Diseases 45
Center Drive, MSC 6600
Bethesda, MD 20892-6600
Telephone: (301) 594-8808
FAX: (301) 480-3503
Email: JOAN_HARMON@NIH.GOV

Susana Serrate-Sztein, M.D.
Arthritis Branch
National Institute of Arthritis, Musculoskeletal and Skin Diseases
Natcher Bldg. Rm 5AS37G
Telephone (301) 594-5032
FAX: (301) 480-4543
Internet: szteins@ep.niams.nih.gov

Anna M. McCormick, Ph.D.
Chief, Biology Branch
Biology of Aging Program
National Institute on Aging
Gateway Building, Suite 2C231
Bethesda, MD 20892
Telephone: (301) 496-6402
FAX: (301) 402-0010
Internet: am38k@nih.gov

Direct inquiries regarding fiscal matters to:

Mrs. Pam Fleming
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases 6003 Executive
Boulevard, Room 4B30
Bethesda, MD 20892-7610
Telephone: (301) 496-7075
FAX: (301) 480-3780
Email: pf49e@nih.gov

Linda Stecklein
Division of Extramural Activities
National Institute of Diabetes and Digestive and Kidney Diseases
Natcher Building, Room 6As-49J
Bethesda, MD 20892-6600
Telephone: (301) 594-8847
FAX: (301) 480-3504
Email: steckleinl@ep.niddk.nih.gov

Ms. Carol Fitzpatrick
Grants Management Branch
NIAMS, NIH
Natcher Bldg. Rm 5AS43K
Telephone: (301) 594-3506
FAX: (301) 480-4543
Internet: fitzpatric@ep.niams.nih.gov

Mr. Joseph Ellis
Grants Management Officer
Grants and Contracts Management Office
National Institute on Aging
Gateway Building, Suite 2N212
Bethesda, MD 20892
Telephone: (301) 496-1472
FAX: (301) 402-3672
Internet: je14j@nih.gov

AUTHORITY AND REGULATIONS

This program is supported under authorization of the Public Health Service Act, Sec. 301(c), Public Law 78-410, as amended. The Catalogue of Federal Domestic Assistance Citations are No. 93.855 - Immunology, Allergy, and Transplantation Research, No. 93.847 - Diabetes, Endocrinology, and Metabolic Diseases, No. 93.846 - Arthritis, Musculoskeletal and Skin Diseases, and No. 93.366 – Aging Research. Awards will be administered under PHS grants policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems review.

The PHS strongly encourage all grant recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or, in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the EPA and PHS missions to protect and advance the physical and mental health of the American people.

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